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Call to arms: need for radiobiology in molecular radionuclide therapy

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Dear Editor,

Now is an extraordinarily exciting time for the multidisciplinary field of molecular radionuclide therapy (MRT) [1-3]. More patients than ever before are being treated with radiolabelled compounds and an increasing number of pharmaceutical companies incorporate radiopharmaceuticals into their portfolios.

MRT allows specific irradiation of localised and disseminated disease with potentially fewer side effects than external beam radiotherapy (EBRT). However, aside from obvious improvements in radiochemistry, radiopharmacy, and dosimetry of MRT agents, a better understanding of the radiobiology, i.e. of the biological effects of ionising radiation of MRT agents, is needed.

Radiobiology has been key in establishing optimal treatment regimens for EBRT whilst protecting healthy tissues. The paradigm of radiobiology is that tumour control probability and side effects are proportional to absorbed radiation dose; radiobiology is thus deeply connected with dosimetry. However, breakthroughs in EBRT effectiveness also required the understanding of concepts that purely fall under radiobiology.

Radiobiology of MRT is necessary to devise an optimised approach of use with regards to activity, therapy interval, vector, radionuclide, combinations, patient selection etc. The frequent ambiguity in predicting treatment outcome and inflexibility in altering set treatment regimens could lead to disease recurrence and avoidable treatment-related side effects that decrease quality of life. For example, it is becoming increasingly clear that some patients are being overtreated (resulting in high levels of toxicity), while some may be under-treated (no tumour regression) [1, 3]. For example, in the NETTER I trial, although most of the patients showed stable disease, very few complete responses were observed [1]. Delivering a radiation dose high enough is necessary. However just this dose parameter might not always be sufficient to best predict treatment efficacy and toxicity [4]. More specifically, a multiparametric approach has to be considered to propose personalized treatments [5].

It is now understood that extrapolation of radiobiology of EBRT to MRT is not straightforward, not only because of differences in dose-rate effects, which would give cells more time to repair lesions, but also because of activation of different molecular and cellular signalling pathways inducing different biological responses [6]. As an MRT radiobiological community, we therefore propose to further deepen our understanding for each therapeutic radiopharmaceutical of the following topics:

Topic 1: **Investigate the consequences of physical parameters** on the tumour and normal tissue response. This includes the role of absorbed radiation dose assessment as a pre-requisite for establishing tumour control and normal tissue complication probability dose-effect curves, just as they exist for EBRT. Dose assessment on the tissue and (sub)cellular scale is essential for determining the role of dose-rate, dose fractionation, and dose distribution [7]. This challenge covers a hugely valuable field, which requires optimisation and standardisation, especially in light of the recent EU directive (European council directive 2013/59 Euratom [7-8]).

Topic 2: **Determine the role of radiopharmaceutical and target distribution** both at the subcellular and tissue level. This includes determining target expression using imaging, (micro) autoradiography, and other techniques, which is a prerequisite for estimating radiotherapy efficacy and toxicity. Non-uniformity of the absorbed dose may lead to increased damage within these subcompartments leading to organ failure. Tissue and subcellular distribution of the radiopharmaceuticals also impacts the choice of the vector (e.g. internalising or not), as well as the subcellular target (e.g. nucleus, cell membrane, mitochondria etc.) and radionuclide (e.g. short or long particle/electron range, high or low LET).

Topic 3: **Determine the role of the tumour microenvironment and systemic reactions** during MRT. As for EBRT, bystander effects and systemic effects involving the immune system (both innate and acquired) may contribute to MRT effectiveness. Bystander effects include intercellular communication between targeted tumour cells (including cancer stem cells) and neighbouring cells including other tumour cells, cancer associated fibroblasts, and endothelial cells [9]. Those

effects will lead to modifications in extracellular matrix structure, in perfusion with consequences on vector distribution and oxygen levels.

Topic 4: **Identify biomarkers of therapy response**. Every patient is unique and tumour characteristics will vary between patients, but also between different metastatic sites within one patient. Currently, every patient receives the same MRT regimen based on their cancer type. To optimize treatment outcome, biomarkers should be identified. These can be simple markers such as target level expression or proliferation, or can be more specific markers such as anomalies in cellular pathways changing radiosensitivity of the tumour or healthy tissues (e.g. DNA damage repair defects).

Topic 5: Determine optimal combination therapies, in particular, combinations of MRT with chemotherapy, immunotherapy, hormone therapy, or radiosensitizers. Combination of EBRT with a variety of these agents is common practice, and several recent (preclinical) studies have shown that MRT effects can be similarly amplified [10].

Topic 6: Determine effects of MRT on healthy tissues, both in the short- and long-term. Radiopharmaceuticals accumulate not only in tumour cells, but also in healthy tissues via normal physiological excretion routes and/or receptor expression on healthy cells. For example, the majority of radiopharmaceuticals are cleared from the body by the kidneys, and radiolabelled PSMA-targeting agents accumulate not only in prostate cancer cells but also in salivary and lacrimal glands.

Our plan of action

We think that a better understanding of the radiobiology of MRT is needed to optimise existing and new MRT strategies to their maximal clinical potential, efficacious in tumour cure whilst simultaneously safe for normal organs. While this includes optimisation of target and vector choice, radiochemistry and dosimetry physics, we aim to expand the field of radiobiology of MRT and form a large collaborative group to ensure clinical impact sooner rather than later. Now is the time to set up national initiatives and create a solid network that connects these at an international level. Hence, this call to arms.

So, calling all researchers in radiobiology and MRT, if you are interested in helping to establish a tight community with the aim to increase the input of radiobiology in existing and new MRT, we propose you to join our working group (www.mrtradiobiology.com), which will foster radiobiology-oriented research in MRT by launching new funded research programs, organizing symposia together with education training.

Partners for whom this would be interesting include radiobiologists, medical physicists, radiochemists, radiopharmacists, nuclear medicine clinicians, radiation oncologists, technologists, referring clinicians, radiation protection advisors, radioactive waste advisors, societies (EANM, ERRS), industry partners, and funding bodies where radiobiology is highlighted as a priority research area.

To conclude, let us invest time, effort and money into this very essential area of nuclear medicine research together.

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